What is claimed is:

1. A pharmaceutical composition comprising a targeted enzyme (TE) and a pharmaceutically acceptable carrier, excipient or diluent, said TE exhibiting a catalytic activity that converts a prodrug to a product and comprising:

a) a substrate recognition site; and

b) a targeting site that binds a target;

wherein

i) the targeting site comprises a variant sequence that is derived from a variation-tolerant sequence of a corresponding pre-targeted enzyme that does not bind the target,

ii) the target is bound by the TE but not by the pre-targeted enzyme under like conditions; and

iii) the target is not an isolated monoclonal antibody.

2. A targeted enzyme exhibiting a catalytic activity that converts a prodrug into a product, comprising:

a) a substrate recognition site;

b) a first targeting site that binds a first target; and

c) a second targeting site that binds a second target,

wherein

i) each targeting site comprises a variant sequence derived from variation-tolerant sequences of a corresponding pre-targeted enzyme, and

ii) the affinity of the targeted enzyme for the first and second target is greater than the affinity of the pre-targeted enzyme for the first and second target under like conditions.

3. The targeted enzyme of Claim 2, wherein the first target and the second target are of a different identity.

4. The targeted enzyme of Claim 2, wherein the first target and second target bind targets of the same identity.

5. The targeted enzyme of Claim 2, wherein at least one of the targeting sites comprises two variant sequences.

6. The targeted enzyme of Claim 5, wherein at least one of the targeting sites comprises three variant sequences.

7. A targeted enzyme exhibiting a catalytic activity that converts a prodrug to a product, comprising:

a) a substrate recognition site; and

b) a targeting site that binds a target,

wherein

i) the targeting site comprises two variant sequences derived from variation-tolerant sequences of a corresponding pre-targeted enzyme,

ii) the affinity of the targeted enzyme for the target is greater than the affinity of the pre-targeted enzyme for the target under like conditions; and

iii) the target is not an isolated monoclonal antibody.

8. A targeted enzyme exhibiting a catalytic activity that converts a prodrug to a product, comprising:

a) a substrate recognition site; and

b) a targeting site that binds a target;

wherein

i) the targeting site comprises three variant sequences, wherein each of the variant sequences is derived from variation-tolerant sequences of a corresponding pre-targeted enzyme; and

ii) the affinity of the targeted enzyme for the target is greater than the affinity of the pre-targeted enzyme for the target under like conditions.

9. A targeted β-lactamase enzyme exhibiting a catalytic activity that converts a prodrug to a product, comprising:

a) a substrate recognition site;

b) a first targeting site that binds a first target;

c) a second targeting site that binds a second target; and

d) a sequence KTXS at its substrate recognition site,

wherein

i) each targeting site comprises a variant sequence derived from a variation-tolerant sequence of a corresponding pre-targeted enzyme, and

ii) the affinity of the targeted enzyme for the first and second target is greater than the affinity of the pre-targeted enzyme for the first and second target under like conditions.

10. A targeted β-lactamase enzyme exhibiting a catalytic activity that converts a prodrug to a product, comprising:

a) a prodrug recognition site;

b) a targeting site that binds a target, and

c) a sequence KTXS at its substrate recognition site,

wherein

i) the targeting site comprises three variant sequences, wherein each of the variant sequences is derived from variation-tolerant sequences of a corresponding pre-targeted β-lactamase enzyme; and

ii) the affinity of the targeted β-lactamase enzyme for the target is greater than the affinity of the pre-targeted β-lactamase enzyme for the target under like conditions.

11. A targeted β-lactamase enzyme exhibiting a catalytic activity that converts a prodrug to a product, comprising:

a) a substrate recognition site;

b) a targeting site that binds a target, and

c) a sequence KTXS at its substrate recognition site,

wherein

i) the targeting site comprises two variant sequences, wherein each of the variant sequences is derived from variation-tolerant sequences of a corresponding pre-targeted β-lactamase enzyme,

ii) the affinity of the targeted β-lactamase enzyme for the target is greater than the affinity of the pre-targeted β-lactamase enzyme for the target, and

iii) the target is not an isolated monoclonal antibody.

12. A pharmaceutical composition comprising a targeted β-lactamase enzyme and a pharmaceutically acceptable carrier, excipient, or diluent, said enzyme exhibiting a catalytic activity that converts a prodrug to a product and comprising:

a) a substrate recognition site;

b) a targeting site that binds a target; and

c) a sequence KTXS at its substrate recognition site,

wherein

i) the targeting site comprises a variant sequence that is derived from a variation-tolerant sequence of a corresponding pre-targeted enzyme that does not bind the target,

ii) the target is bound by the targeted β-lactamase enzyme but not by the pre-targeted β-lactamase enzyme under like conditions, and

iii) the target is not an isolated monoclonal antibody.

13. The targeted enzyme of Claim 1 or 12, wherein the targeted enzyme binds the prodrug via the substrate recognition site.

14. The pharmaceutical composition of Claim 13, wherein the targeted enzyme cleaves the prodrug.

15. A method of ameliorating a symptom of a disease in a subject in need of symptom amelioration, comprising

a) administering to said subject a therapeutically effective amount of the targeted enzyme of one of Claims 1 or 12 for a time sufficient to allow the targeted enzyme to bind a target; and

b) administering an amount of said prodrug to said subject such that a sufficient amount of said prodrug is converted to an active drug that a symptom of the disease is ameliorated.

16. The method of Claim 15, wherein the targeted enzyme cleaves said prodrug to release the active drug.

17. The method of Claim 15, wherein the targeted enzyme has a molecular weight of less than about 45,000 Daltons.

18. The method of Claim 15, wherein the targeted enzyme does not act directly on the prodrug.

19. The method of Claim 15, wherein the targeted enzyme is a β-lactamase.

20. The method of Claim 15, wherein the targeted enzyme is a protease.

21. The method of Claim 15, wherein the disease is a cell proliferative disorder, an autoimmune disease, or an infectious disease.

22. The method of Claim 21, wherein the cell proliferative disorder is a cancer.

23. The method of Claim 15, wherein the prodrug is a cephalosporin.

24. The method of Claim 15, wherein the drug is a chemotherapeutic drug.

25. The method of Claim 15, wherein the targeted enzyme has a modification and an decreased host immune response relative to that of a corresponding unmodified targeted enzyme.

26. The method of Claim 15, wherein the targeted enzyme is less than about 45,000 Daltons.

27. The method of Claim 15, wherein the targeted enzyme is administered systemically.

28. The method of Claim 15 wherein the target is a cell surface molecule.

29. The method of Claim 28, wherein the cell surface molecule is a tumor cell surface molecule.